highly similar. (Fig. 8A) Rat intron sequences corresponding to previously reported 21 nucleotide human sequence, IAS 2, which also mediates IIIb activation contain only one nucleotide difference (SEQ ID NOs:45 and 46, respectively). (Fig. 8B) The 57 nucleotide rat ISAR sequence (SEQ ID NO:34) is highly similar to human sequences (SEQ ID NO:47) in this same region, including the 18 nt shown to be most important for regulation (boxed sequences).

Please replace the paragraph beginning at page 12, line 21, with the following rewritten paragraph:

FIG. 9. Depiction of a model which can account for results and the high fidelity of FGF-R2 splicing. AT3 cells use a default splicing pathway and choose the IIIc exon because of its stronger polypyrimidine tract (ppt), they splice IIIb inefficiently due to its weaker polypyrimidine tract. DT3 cells require regulatory factor(s) which can activate (+) the weaker IIIb exon and at the same time repress use of the IIIc exon. The ISAR element (indicated by the hatched box) is shown binding a factor or complex of factors (large shaded oval) which mediates both of these effects. The previously demonstrated contributions of other

cis-elements and associated factors (smaller shaded ovals) on IIIb activation are also shown, as well as the suggestion of possible cooperative interaction between proteins bound at several locations within the intron. Abbreviations are defined in the description to Fig. 3.

Please replace the paragraph beginning at page 13, line 15, with the following rewritten paragraph:

C3

Progression of human prostate cancer from an androgen sensitive to an androgen insensitive tumor is accompanied by a change in alternative splicing of FGF-R2. This change results in a loss of the FGF-R2 IIIb isoform and predominant expression of the FGF-R2 IIIc isoform. This event provides an important biological marker for progression of prostate cancer.

Please replace the paragraph beginning at page 31, line 19, with the following rewritten paragraph:

C4

Sequences between the Nde I and Nsi I sites mediate regulation in DT3 cells by activating use of the upstream IIIb exon as well as by repressing use of the downstream IIIc exon. The results obtained with deletions in intron 2 suggested that the requirements for exon IIIc inclusion in

AT3 cells are less stringent than those for IIIb inclusion in DT3 cells. In fact, with the sets of minigenes no intronic sequences outside of the conserved splice junctions or polypyrimidine tract were observed which impeded splicing of IIIc in AT3 cells. This is not surprising given the stronger polypyrimidine tract associated with the IIIc exon when compared to that of IIIb. Thus, while the possibility exists that there are other untested intron sequences or exon IIIc sequences which interact with AT3 cell-specific factors to mediate IIIc inclusion in these cells, it is expected that IIIc exon inclusion is a default splicing pathway which may only require the cooperation of factors involved in the constitutive splicing process. Thus, regulation may be achieved by proteins in DT3 cells which are able to switch the splicing pattern from exon IIIb to IIIc. Consistent with this view are the observations that several of the deletions caused not only skipping of both exons, but also a switch towards some IIIc inclusion. Therefore, if FGF-R2 mutually exclusive alternative splicing is predominantly regulated only in DT3 cells, the sequences which are involved in this regulation could be acting by activating IIIb splicing, repressing IIIc splicing, or by performing both of these functions. To investigate these alternatives,

a series of minigenes were constructed in which either IIIb or IIIc (but not both) was inserted into pI-11 and the previous deletions were used in such a manner that IIIb was inserted either with (pI-11-IIIb-plus) or without (pI-11-IIIb-minus) the Nde I to Nsi I sequences located downstream, and IIIc was inserted with (pI-11-IIIc-plus) or without (pI-11-IIIc-minus) these same sequences upstream (Fig. 5A). Because these minigenes only offered a choice of including an internal exon or skipping, the use of the internal IIIb or IIIc exon was quantified vs. that of the skipped product. As shown in Fig. 5B, when these minigenes were transfected into AT3 cells, the IIIc exon was included highly efficiently, and this inclusion was not affected by the presence of the Nde I to Nsi I sequences located upstream. In addition, AT3 cells did not include exon IIIb efficiently and this effect was essentially unchanged whether or not these sequences were located downstream. In DT3 cells, on the other hand, IIIb inclusion was seen to occur with fairly high efficiency, but this inclusion was largely dependent on the presence of the Nde I to Nsi I sequence located downstream; when this sequence was deleted IIIb inclusion was dramatically reduced from 68% to only 13%. In addition, it was noted that when the Nde I to Nsi I sequences were present upstream of IIIc, DT3 cells included

IIIc rarely, but when these sequences were deleted, the proportion of IIIc included approximately tripled, from 11% to 35%. This data was consistent with a model in which regulation of FGF-R2 alternative splicing in DT3 cells is achieved by the interaction of a cell-specific factor or complex of factors that interact with intronic sequences in intron 2 and coordinated activation of exon IIIb splicing and repression of the stronger IIIc exon. The fact that the sequences between Nde I and Nsi I were necessary for both of these effects to occur resulted in this sequence being designated ISAR (Intronic Splicing Activator and Repressor) and indicated that this element is required for the formation of a regulatory complex which acts in DT3 cells to force the use of IIIb instead of IIIc. (The sequence between exons IIIb and IIIc is set forth in Fig. 10 (rat) and Fig. 11 (human)).

Substitute the Sequence Listing submitted herewith for the Sequence Listing filed August 12, 2002.

IN THE CLAIMS:

Add the following new claims.

6. (New) A method of assessing the androgen sensitivity of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIc isoform mRNA, wherein expression of the FGF-R2 IIIc isoform mRNA correlates with androgen insensitivity.

7. (New) A method of determining the likelihood of metastasis of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIb isoform mRNA, wherein lack of expression of the FGF-R2 IIIb isoform mRNA indicates said tumor is likely to metastasize.

8. (New) A method of assessing androgen sensitivity of a prostate tumor in a human patient comprising assaying said tumor for FGF-R2 IIIb isoform mRNA, wherein lack of expression of the FGF-R2 IIIb isoform mRNA correlates with androgen insensitivity.

IN THE DRAWINGS:

Revise Figures 6A, 8A and 8B to include sequence identifiers in the manner noted in red in the copies of those Figures submitted herewith on separate sheets.